PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1128WOORD01		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/08724	06.08.2003	10.08.2002

International Patent Classification (IPC) or both national classification and IPC

A61K31/502, A61K31/502

Applicant

ALTANA PHARMA AG et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.02.2004	15.06.2004

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/08724

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-39 as originally filed

Claims, Numbers

1-22 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 19-22

   because:

   ☒ the said international application, or the said claims Nos. 19-22 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-22
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item I

Basis of the opinion

The application is directed to

(i) the first medical use of compounds (1) (claims 1-2, 14-15),
(ii) the second medical use of compounds (1) (claim 3, 14-15),
(iii) compounds (1) (claims 4-7, 11-15),
(iv) the first medical use of further compounds (1) (claim 8, 14-15),
(v) the second medical use of further compounds (1) (claim 9, 14-15),
(vi) further compounds (1) (claim 10 and 14-15),
(vii) the first medical use of compounds (1) of claims 4 and 10 (claim 16),
(viii) a pharmaceutical composition comprising compounds (1) of claims 4 and 10 (claim 17),
(ix) the second medical use of compounds (1) of claims 4 and 10 (claim 18),
(x) the corresponding therapeutic methods (independent claims 19-22).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1 Claims 19-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents.

D1: WO 02/085906 A, 31.10.2002; cited in the application.
D2: WO 02/064584 A, 22.08.2002; cited in the application.
D3: WO 01/94319 A, 13.12.2001; cited in the application.
D4: WO 98/31674 A, 23.07.1998; cited in the application.

Documents D1 and D2 were published after the priority date. Under the presumption that the priority is valid for the claimed matter these documents are

not considered as prior art under Rule 64.1 PCT.

2 Novelty

2.1 **D3** relates inter alia to piperidinyl-phthalazones as combined beta-2-adrenoceptor agonists and PDE4 inhibitors from which the present compounds (1) differ through the absence of the Ar_2 moiety (cf. D3, claim 1). Furthermore, the document discloses H_2N-$(CH_2)_2$-C(O)-, H_2N-$(CH_2)_2$-S-$(CH_2)_2$-C(O)-, and H_2N-$(CH_2)_2$-SO_2-$(CH_2)_2$-C(O)-substituted intermediates **5a**, **14a**, and **15a** from which the present compounds (1) differ insofar as R^{13} and R^{16} of the group R^9 are different from NH_2. The present claimed matter is thus novel vis-à-vis D1.

D4 discloses PDE4-inhibiting 2-substituted phthalazones wherein the 2-substituent inter alia represents N-methylpiperidinyl. The present claimed matter is novel over D4 through the N-piperidinyl substituent R^9 of the compounds (1).

In view of D3 and D4 the application complies with the criterion of novelty.

2.2 **D1** discloses PDE4-inhibiting N(R^{13})-substituted piperidinyl-phthalazones (cf. claim 1, when R^5 is R^{12}; and example 4 with R^{13} = pyridin-4-ylmethyl), which overlap with the present compounds (1) at least when R^9 = -Y-$(CH_2)_q$-Z-$(CH_2)_r$-R^{16} with Y = CO, Z = bond, and R^{16} = amino, mono- or di-C_{1-4}alkylamino (cf. D1, claim 1, R^{13} = C(O)-$(CH_2)_r$-N(R^{20})R^{21}).

D2 discloses also PDE4-inhibiting N(R^9)-substituted piperidinyl-phthalazones which overlap with the present compounds (1) when R^9 = -Y-$(CH_2)_q$-Z-$(CH_2)_r$-R^{18} with Y = CO, Z = bond, and R^{16} = hydrogen (cf. D2, claim 1, R^9 = -C(O)R^{13}, R^{13} = C_{1-4}alkyl; and example 3 with R^9 = -C(O)CH_3), amino, mono- or di-C_{1-4}alkylamino (cf. D2, claim 1, R^9 = C(O)-$(CH_2)_n$-N(R^{16})R^{17}).

D1 and **D2** may, thus, become relevant to the question of novelty of present claims 8-10 and 16-18 in the regional phase. In the present independent claims 1-3 the overlapping range with D1 and D2 is excluded by a disclaimer. However, in case the present claimed priority would not be valid the documents may also become relevant to the questions of inventive step and unity of the application.

3 Inventive Step

3.1 The application describes the synthesis of certain compounds (1) and indicates that such compounds represent PDE4 inhibitors (the application page 39).

3.2 Starting from D3 or D4 as most relevant state of the art, the problem underlying the present application may be seen in the provision of further PDE4 inhibitors. Due to the fact that the documents D3 and D4 teach merely piperidinyl-phthalazones as PDE4 inhibitors with very specific piperidinyl-N-substituents (i.e. D4: N-methyl-piperidinyl; and D3: a substituent -NH-CH(R^8)C(Ar_2)OH; see e.g. page 42, the product of reaction 10) it does not appear unequivocally obvious that the present claimed compounds would retain the desired activity. Consequently, in view of only D3 and D4 an inventive step may be acknowledged for the present claims 1-22.

4 Industrial Applicability

For the assessment of the present claims 19-22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5 Deficiencies of the Application under 6 PCT

The present set of claims is objected under Article 6 PCT for lack of conciseness, because the first medical use claims 1, 8, and 16; the second medical use claims 3, 9, and 18; and the product claims 4 and 10 are drafted as separate independent claims in the same category, although they relate basically to identical subject matter in each category. Furthermore, in the second medical use claims 3 and 9 the therapeutic application is only functionally defined by a mechanism of action which does not allow any practical application in the form of a defined, real treatment of a pathological condition. This objection could be overcome by either introducing in the claims a list of pathological conditions (diseases) cited in the application, or by showing that means are available which would allow the skilled person to recognise which additional condition(s) would fall within the functional definition.

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